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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,000	SOOD ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *57-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 1-56, in the reply filed on 7/26/2006 is acknowledged.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claim1-7, 9, 11-13, 15-18, 20, 30-38, 40, 42-45, 47, 55, 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al (WO/2001/94609).

As the specification does not define "polyphosphate", the broadest reasonable is 3 or more phosphate groups, which reads on nucleotide triphosphates.

With regards to claim 1, Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached"

(See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates.

With regards to claim 2, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21). Target nucleic acid is interpreted as template.

With regards to claim 3, Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19). Williams teaches oligonucleotides are primers (see page 29, lines 7-18).

With regards to claim 4, Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2).

With regards to claim 5, Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6).

With regards to claim 6, Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29).

With regards to claim 7, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). The amount of pyrophosphate released is thus proportional to the amount of template nucleic acid present. The amount of nucleic acid present is thus quantitated.

With regards to claim 9, Williams teaches a nucleic acid polymerase (see page 4 lines 20-21).

With regards to claims 11 and 12, Williams teaches DNA as a template (see abstract). Instant specification teaches, "'oligonucleotide' includes linear oligomers of nucleotides or derivatives thereof, including deoxyribonucleosides." Oligonucleotide thus encompasses DNA.

With regards to claim 13, Williams teaches sequencing in real time (see abstract). Real time sequencing requires the conducting step and subjecting step to be done simultaneously.

With regards to claim 15, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). As Williams teaches the pyrophosphate has the detectable label, this is interpreted as detectable species directly proportional to mount of nucleic acid sequence.

With regards to claim 16, Williams teaches the use other phosphate transferring enzymes that include ATP sulphurylase-luciferase system and phosphatase.

With regards to claim 17, Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6).

With regards to claim 18, Williams teaches the nucleotide sequence of the target DNA can be thereafter be directly read from the order of releases dyes attached to pyrophosphate (see page 24, lines 7-8).

With, regards to claim 20, Williams teaches use of fluorescent dyes (see page 24, lines 5-6).

The addition of terminal phosphate labeled polyphosphates in claims 30 and 31 is interpreted as the incorporation into primer elongation.

With regards to claims 30, 31, 55 and 56, Williams teaches sequencing the target nucleic acid (see page 4, lines 28-29). Sequencing is based on the addition of nucleotides or nucleoside polyphosphates in order to make a complementary strand of the target region. The sequencing method taught by Williams encompasses this, further Williams teachings of the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6) results in sequencing by addition of labeled bases.

With regards to claim 32, Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate

(NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15).

With regards to claim 33, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21). Target nucleic acid is interpreted as template.

With regards to claim 34, Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19). Williams teaches oligonucleotides are primers (see page 29, lines 7-18).

With regards to claim 35, Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2).

With regards to claim 36, Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6).

With regards to claim 37, Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29).

With regards to claim 38, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). The amount of pyrophosphate released is thus proportional to the amount of template nucleic acid present. The amount of nucleic acid present is thus quantitated.

With regards to claim 40, Williams teaches a nucleic acid polymerase (see page 4 lines 20-21).

With regards to claims 42 and 43, Williams teaches DNA as a template (see abstract). Instant specification teaches, "'oligonucleotide' includes linear oligomers of nucleotides or derivatives thereof, including deoxyribonucleosides." Oligonucleotide thus encompasses DNA.

With regards to claim 44, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). As Williams teaches the pyrophosphate has the detectable lable, this is interpreted as detectable species directly proportional to mount of nucleic acid sequence.

With regards to claim 45, Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6).

With, regards to claim 47, Williams teaches use of fluorescent dyes (see page 24, lines 5-6).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 8 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Wittwer et al (US Patent 6174670).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams does not teach quantifying nucleic acid by comparing spectra with a known standard.

However, Wittwer teaches determining the concentration of a nucleic acid by comparison to the fluorescence of a known concentration template (see column 11, line 65 to column 12 line 40). Wittwer teaches this simple method allows quantification of low copy number DNA (see column 39, lines 59-60).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to quantitate the nucleic acid sequences of Williams with Wittwers method of quantitation, because Wittwer teaches it is a simple method for quantification of low copy number DNA. The ordinary artisan would be motivated to improve Williams method of sequencing because Wittwer teaches a simple method for quantification of low copy number DNA.

5. Claim 10 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Keller et al (US Patent 5656462).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25,

lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams does not teach the use of an RNA template.

However, Keller et al teaches the use of an RNA template (see column 13, lines 54-55) because it is useful in the preservation and analysis of genes.

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to improve Williams method of sequencing by the use of RNA templates as taught by Keller, because Keller teaches use of RNA allows gene analysis. The ordinary artisan would be motivated to use the RNA template, because Keller teaches the RNA template is useful in preservation and analysis of genes.

6. Claim 19 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Lichenwalter et al (US Patent 5683875).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid"

(see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6). Williams does not teach the use of an antibody as a detection reagent.

However, Lichtenwalter et al teach the use of an antibody to detect elongated nucleic acid complexes (see column 3, lines 27-30, column 3, lines 14-17), because it is a convenient and reliable diagnostic method (column 13, lines 20-21).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to use the antibodies taught by Lichtenwalter to detect the elongation products of Williams, because Lichtenwalter teaches it is a convenient and reliable diagnostic method. The ordinary artisan would be motivated to detect Williams elongation products with Lichtenwalter's antibodies because Lichtenwalter teaches it is a convenient and reliable diagnostic method.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-5, 9-12, 16-18, 20, 30-36, 40-45, 47, 55, 56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 12, 14, 16, 17, 25 of copending Application No. 11/255683. Although the conflicting claims are not identical they are coextensive in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. Claim 1 of '683 teaches a method of sequencing on a solid support by polymerization and detection of a reaction product. Claim 14 of '683 teaches the use of a terminal phosphate nucleotide. Claim 20 of '683 teaches the use of a phsophatase. Application '683 thus teaches sequencing on a

solid support by detecting the release of a terminally labeled polyphosphate and phosphatase.

Claims 2 and 3 of instant application is drawn to a primer or a nucleic acid template immobilized on a solid support. Claim 2 of '683 teaches primer template combination attached to a solid structure. The primer template complex solid complex requires either the template or primer to be attached to the solid support, therby immobilizing both the primer and template.

Claim 4 of instant invention is to the primer nucleic template being hybridized before immobilized. Claim 25 of '683 teaches primed nucleic acid templates are formed prior to immobilization on said slid support.

Claim 5 of instant application is drawn to a nucleic acid polymerization enzyme being attached in a solid support. Claim 3 of '683 teaches the use of polymerase colony technology which requires the polymerase to be attached to a slide.

Claim 9 of instant application is drawn to a polymerase. Claim 12 of '683 teaches the use of a DNA polymerase.

Claim 10 of instant application is drawn to a RNA template. Claim 12 of '683 teaches the use of a reverse transcriptase which requires RNA as a template.

Claim 11 and 12 of instant application is drawn to a DNA template. Claim 12 of '683 teaches the use of DNA polymerase which requires DNA as a template. DNA is a natural or synthetic oligonucleotide.

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. Claim 20 of '683 teaches the use of a phophatase,

claim 22 teaches the use of ATP sulfuryase which is a phosphate transferring enzyme. ATP sulfurylase transfers polyphosphate to produce ATP.

Claim 17 of instant application is drawn to including one of more detectable agents in the polymerization reaction. Claim 16 of '683 teaches the use of 4 nucleotides carrying distinct labels.

Claim 18 of instant application is drawn to one or more additional detection reagents detectably different. Claim 16 of '683 teaches the use of 4 nucleotides carrying distinct labels. The distinct labels are interpreted as detectably different.

Claim 20 of instant application is drawn to detectable species from the group of color, fluorescence emission, chemiluninescence. Claim 17 of '683 teaches fluorescent dyes, colored dyes, or chemiluminescent dyes.

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. claim 1 and 14 of '683 teaches sequencing with a terminal phosphate labled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 1 and 14 of '683 teaches sequencing with a terminal phosphate labeled nucleotide. The use of 4 distinctly labeled bases taught in claim 14 of '683 results in a reaction in which all nucleotides are added to the reaction mix at once, which is a preset cycle.

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. The detection allows determination of nucleotide sequences. Claim 1 of '683 teaches a method of sequencing on a solid support by polymerization and detection of a reaction product. Claim 14 of '683 teaches the use of a terminal phosphate nucleotide. Application '683 thus teaches sequencing on a solid support by detecting the release of a terminally labeled polyphosphate and phosphatase.

Claims 33 and 34 of instant application is drawn to a primer or a nucleic acid template immobilized on a solid support. Claim 2 of '683 teaches primer template combination attached to a solid structure. The primer template complex solid complex requires either the template or primer to be attached to the solid support, thereby immobilizing both the primer and template.

Claim 35 of instant invention is to the primer nucleic template being hybridized before immobilized. Claim 25 of '683 teaches primed nucleic acid templates are formed prior to immobilization on said slid support.

Claim 36 of instant application is drawn to a nucleic acid polymerization enzyme being attached in a solid support. Claim 3 of '683 teaches the use of polymerase colony technology which requires the polymerase to be attached to a slide.

Claim 40 of instant application is drawn to a polymerase. Claim 12 of '683 teaches the use of a DNA polymerase.

Claim 41 of instant application is drawn to a RNA template. Claim 12 of '683 teaches the use of a reverse transcriptase which requires RNA as a template.

Claim 42 and 43 of instant application is drawn to a DNA template. Claim 12 of '683 teaches the use of DNA polymerase which requires DNA as a template. DNA is a natural or synthetic oligonucleotide.

Claim 44 of instant application is drawn to the use of one or more detection agents. Claim 16 of '683 teaches the use of 4 nucleotides carrying distinct labels.

Claim 45 of instant application is drawn to one or more additional detection reagents detectably different. Claim 16 of '683 teaches the use of 4 nucleotides carrying distinct labels. The distinct labels are interpreted as detectably different.

Claim 47 of instant application is drawn to detectable species from the group of color, fluorescence emission, chemiluninescence. Claim 17 of '683 teaches fluorescent dyes, colored dyes, or chemiluminescent dyes.

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 1 and 14 of '683 teaches sequencing with a terminal phosphate labdled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 1 and 14 of '683 teaches sequencing with a terminal phosphate labeled nucleotide. The use of 4 distinctly labeled bases taught in claim 14 of '683 results in a

reaction in which all nucleotides are added to the reaction mix at once, which is a preset cycle.

9. Claims 1-6, 9, 11-37, 38, 40, 42, 44, 45, 47-56 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-8,10-12, 15-22, 25, 28, 29 of U.S. Patent No. 7041812 in view of Williams et al (WO/2001/94609). Although the conflicting claims are not identical, they are coextensive in scope.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. Claims 15 and 22 of '812 teach a method of sequencing by polymerization and detection of a reaction product. Claim 16 of '812 teaches the use of a phosphate or polyphosphate transferring enzyme.

Claim 9 of instant application is drawn to a polymerase. (Claim 15 of '812). Claim 11 and 12 of instant application is drawn to a DNA template. Claim 15 of '812 teaches the use of DNA polymerase which requires DNA as a template. DNA is a natural or synthetic oligonucleotide.

Claim 14 of instant application is drawn to polyphosphates with 4 or more phosphates in the polyphosphate chain. (Claim 19 and claim 20 of '812).

Claim 15 of instant application is drawn to the detectable species produced being substantially proportional to the amount of nucleic acid sequence. (Claim 22 of '812).

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. Claim 16 of '812 teaches the use of a of a polyphosphate transferring enzyme, which is a phosphatase.

Claim 17 of instant application is drawn to including one of more detectable agents in the polymerization reaction. (Claim 17 of '812).

Claim 18 of instant application is drawn to one or more additional detection reagents detectably different. Claim 17 of '812 teaches the use of 2 or more terminal phosphate labeled nucleotides with distinct labels. The distinct labels are interpreted as detectably different.

Claim 19 of instant application is drawn to the use of an antibody as a detection reagent. (Claim 25 of '812).

Claim 20 of instant application is drawn to detectable species from the group of consisting of color, fluorescence emission, chemiluminescence, mass change, reduction/oxidation potential and combinations thereof. (Claim 18 of '812).

Claim 21 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 19 of '812).

Claim 22 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 18 of '812).

Claim 23 of instant application is drawn to fluorogenic dyes. (Claim 6 of '812).

Claim 24 of instant application is drawn to 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate or derivative thereof. (Claim 8 of '812).

Claim 25 of is drawn to a phosphatase activated 1, 2-dioxetane compound. (Claim 9 of '812.)

Claim 26 of instant application 2-chloro-5-(4-methoxyspiro[1,2-diox- etane-3,2'-(5-chloro-)tricyclo[3,3,1-1.sup.3,7]-decan]-1-yl)-1-phenyl phosphate, chloroadamant-2'-ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,- 2-dioxetane and derivatives thereof. (Claim 10 of '812).

Claim 27 of instant application is drawn to modified sugars. (Claims 11 and 28 of '812).

Claim 28 of instant application is drawn to a sugar moiety of ribosyl or 2'-deoxyribosyl sugar. (Claims 11 and 28 of '812)

Claim 29 of instant application is drawn to nucleotide analogs. (Claims 12 and 29 of '812.)

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 15 of '812 teaches the ordered incorporation of nucleotides.

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. claim 15 and 17 of '812 teaches sequencing with a terminal phosphate labeled nucleotide. The use of at least 2 distinctly labeled bases taught in claim 17 of '812 results in a reaction in which all nucleotides are added to the reaction mix at once, which is a preset cycle.

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. The detection allows determination of nucleotide sequences. Claims 15 and 22 of '812 teach a method of sequencing by polymerization and detection of a reaction product.

Claim 38 of instant application is drawn to quantifying a nucleic acid sequence. (Claim 21 of '812).

Claim 40 of instant application is drawn to a polymerase. (Claim 15 of '812).

Claim 42 and 43 of instant application is drawn to a DNA template. Claim 15 of '812 teaches the use of DNA polymerase which requires DNA as a template. DNA is a natural or synthetic oligonucleotide.

Claim 44 of instant application is drawn to the use of one or more detection reagents. (Claim 17 of '812).

Claim 45 of instant application is drawn to one or more additional detection reagents detectably different. Claim 17 of '812 teaches the use of 2 or more terminal phosphate labeled nucleotides with distinct labels. The distinct labels are interpreted as detectably different.

Claim 47 of instant application is drawn to detectable species from the group of color, fluorescence emission, chemiluninescence. (Claim 18 of '812).

Claim 48 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 19 of '812.)

Claim 49 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 18 of '812).

Claim 50 and 51 of instant application is drawn to a colored dye selected from the group consisting azo dye, a merrocyanine, a cyanine dye, a xanthene dye, a porphyrin dye, a coumarin dye, a bodipy dye and derivatives thereof. (Claim 7 of '812)

Claim 52 of instant application is drawn to ribosyl, 2'-deoxyribosyl, 3'-deoxyribosyl, 2',3'-didehydrodideoxyribosyl, 2',3'-dideoxyribosyl, 2'-alkoxyribosyl, 2'- or 3'-azidoribosyl, 2'- or 3'-aminoribosyl, 2'- or 3'-fluororibosyl, 2'-mercaptoribosyl, 2'-alkylthioribosyl, carbocyclic, acyclic and other modified sugars. (Claim 11 of '812)

Claim 53 of instant application is drawn to a sugar moiety of ribosyl or 2'-Claim deoxyribosyl sugar. (Claims 11 and 28 of '812).

Claim 54 of instant application is drawn to nucleotide analogs. (Claims 12 and 29 of '812).

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. (Claim 17 of '812).

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. (Claim 17 of '812).

'812 does not teach the a nucleic acid template immobilized on a solid support (claim1, 2, 32,33), a primer immobilized on a solid support (claim 1, 3, 32, 34), a primer

and template hybridized then immobilized on a solid support (claim 1, 4, 32, 34), a polymerization enzyme on solid support (claim 5, 36), or a flow through system (claim 6, 37).

However, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21)(claims 1, 2, 32, 33). Target nucleic acid is interpreted as template. Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19) (claims claim 1, 3, 32, 34). Williams teaches oligonucleotides are primers (see page 29, lines 7-18). Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2) (claim 1, 4, 32, 34). Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6) (claims 5 and 36). Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29) (claims 6 and 37). Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides (see abstract).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of immobilization and flow cells taught by Williams to improve the methods of detection taught by US Patent 7041812, because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides. The ordinary artisan would be motivated to use the flow cell and immobilization of Williams because Williams teaches the flow cell and immobilization of reaction

components allows for real time sequencing without interference from unincorporated nucleotides.

10. Claims 1-6, 9-34, 38, 40-45, 47-49, 52-56 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-10, 12-14, 16-19, 21-24, 26, 44-46, 67-68 of U.S. Patent No. 7052839 in view of Williams et al (WO/2001/94609). Although the conflicting claims are not identical they are coextensive in scope.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. (claim 1 of '839).

Claim 9 of instant application is drawn to a polymerase. (Claim 1 of '839).

Claim 10 of instant application is drawn to RNA as the nucleic acid template. (Claim 3 of '839).

Claim 11 and 12 of instant application is drawn to a DNA template. Claim 12 of '839 teaches the use of DNA and claim 12 teaches use of synthetic or natural oligonucleotide.

Claim 13 of instant application is drawn to the simultaneous conducting and subjecting steps. Claim 2 of '839 teaches the polymerase reaction in the presence of a phosphatase, which would result in simultaneous conducting and subjecting steps.

Claim 14 of instant application is drawn to polyphosphates with 4 or more phosphates in the polyphosphate chain. (Claim 7 of '839).

Claim 15 of instant application is drawn to the detectable species produced being substantially proportional to the amount of nucleic acid sequence. (Claim 9 of '839).

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. (Claim 2 of '839)

Claim 17 of instant application is drawn to including one of more detectable agents in the polymerization reaction. (claim 17 of '839).

Claim 18 of instant application is drawn to one or more additional detection reagents detectably different. (Claim 4 of '839).

Claim 19 of instant application is drawn to the use of an antibody as a detection reagent. (Claim 16 of '839).

Claim 20 of instant application is drawn to detectable species. (Claim 17 of '839).

Claim 21 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 6 of '839).

Claim 22 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 18 of '839).

Claim 23 of instant application is drawn to fluorogenic dyes. (Claim 19 and 42 of '839).

Claim 24 of instant application is drawn to 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate or derivative thereof. (Claims 20 and 43 of '839).

Claim 25 of instant application is drawn to a phosphatase activated 1, 2-dioxetane compound. (Claims 21 and 44 of '839)

Claim 26 of instant application 2-chloro-5-(4-methoxyspiro[1,2-diox- etane-3,2'-(5-chloro-)tricyclo[3,3,1-1.sup.3,7]-decan]-1-yl)-1-phenyl phosphate, chloroadamant-2'-ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,- 2-dioxetane and derivatives thereof. (Claim 22 and 45 of '839).

Claim 27 of instant application is drawn to modified sugars. (Claims 23, 46, and 67 of '839)

Claim 28 of instant application is drawn to a sugar moiety of ribosyl or 2' deoxyribosyl sugar. (Claims 23, 46, and 67 of '839).

Claim 29 of instant application is drawn to nucleotide analogs. Claims 24,57, 68 of '839).

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 1 of '839 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule.

Claim 1 of '839 teaches sequencing with a terminal phosphate labeled nucleotide. The use of at least 2 distinctly labeled bases taught in claim 4 of '839 results in a reaction in which all nucleotides are added to the reaction mix at once, which is a preset cycle.

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. Claims 1 and 26 of '839 teach a method of sequencing by polymerization and detection of a reaction product.

Claim 38 of instant application is drawn to quantifying a nucleic acid sequence. (Claim 49 of '839).

Claim 40 of instant application is drawn to a polymerase. (Claim 13 of '839).

Claim 41 of instant application is drawn to RNA as the nucleic acid template. (Claim 3 of '839).

Claim 42 and 43 of instant application is drawn to a DNA template. Claim 12 of '839 teaches the use DNA as a template. Claim 10 of '839 teaches natural or synthetic oligonucleotide.

Claim 44 of instant application is drawn to the use of one or more detection reagents. Claim 4 of '839 teaches the use of 2 or more terminal phosphate labeled nucleotides with distinct labels.

Claim 45 of instant application is drawn to one or more additional detection reagents detectably different. Claim 4 of '839 teaches the use of 2 or more terminal

phosphate labeled nucleotides with distinct labels. The distinct labels are interpreted as detectably different.

Claim 47 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 18 of '839).

Claim 48 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 6 of '839).

Claim 49 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 18 of '839).

Claim 52 of instant application is drawn modified sugars. Claims 23, 46, 56 of '839).

Claim 53 of instant application is drawn to a sugar moiety of ribosyl or 2'-Claim deoxyribosyl sugar. (Claims 23, 46, 56 of '839)

Claim 54 of instant application is drawn to nucleotide analogs. (Claims 24, 57 of '839).

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 1 of '839 teaches the ordered incorporation of nucleotides.

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 1 of '839 teaches sequencing with a terminal phosphate labeled nucleotide.

US Patent 7052839 does not teach the a nucleic acid template immobilized on a solid support (claim1, 2, 32,33), a primer immobilized on a solid support (claim 1, 3, 32, 34), a primer and template hybridized then immobilized on a solid support (claim 1, 4, 32, 34), a polymerization enzyme on solid support (claim 5, 36), or a flow through system (claim 6, 37).

However, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21)(claims 1, 2, 32, 33). Target nucleic acid is interpreted as template. Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19) (claims claim 1, 3, 32, 34). Williams teaches oligonucleotides are primers (see page 29, lines 7-18). Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2) (claim 1, 4, 32, 34). Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6) (claims 5 and 36). Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29) (claims 6 and 37). Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides (see abstract).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of immobilization and flow cells taught by Williams to improve the methods of detection taught by US Patent 7052839, because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides.

The ordinary artisan would be motivated to use the flow cell and immobilization of Williams because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides.

11. Claims 1-6, 9-18, 20-38, 40-46, 48, 49, 52-56 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 19, 22-30, 35-37, 39-40 of U.S. Patent No. 7033762 in view of Williams et al (WO/2001/94609). Although the conflicting claims are not identical they are coextensive in scope.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. Claim 22 of '762 teaches a method of sequencing by polymerization and detection of polyphosphate. Claim 22 of '762 teaches the use of a phosphatase or polyphosphate transferring enzyme.

Claim 9 of instant application is drawn to a polymerase. (Claim 22 of '762).

Claim 10 of instant application is drawn to RNA as the nucleic acid template. (Claim 26 of '762).

Claim 11 of instant application is drawn to a DNA template. Claim 26 of '762.

Claim 12 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 26 of '762 teaches the use of DNA as a template. DNA is a natural or synthetic oligonucleotide.

Claim 13 of instant application is drawn to the simultaneous conducting and subjecting steps. Claim 23 of '762 teaches the polymerase reaction in the presence of a phosphatase, which would result in simultaneous conducting and subjecting steps.

Claim 14 of instant application is drawn to polyphosphates with 4 or more phosphates in the polyphosphate chain. (Claim 30 of '762).

Claim 15 of instant application is drawn to the detectable species produced being substantially proportional to the amount of nucleic acid sequence. (Claim 24 of '762).

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. (Claim 22 of '762).

Claim 17 of instant application is drawn to including one of more detectable agents in the polymerization reaction. (Claim 27 of '762).

Claim 18 of instant application is drawn to one or more additional detection reagents detectably different. Claim 27of '762 teaches the use of 2 or more terminal phosphate labeled nucleotides with distinct labels, distinct labels are interpreted as detectably different.

Claim 20 of instant application is drawn to detectable species. (Claim 28 of '762).

Claim 21 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 29 of '762).

Claim 22 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 29 of '762)

Claim 23 of instant application is drawn to fluorogenic dyes. (Claim 35 of '762).

Claim 24 of instant application is drawn to 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate or derivative thereof. (Claim 36 of '762)

Claim 25 of instant application is drawn to a phosphatase activated 1, 2-dioxetane compound. (Claim 37 of '762).

Claim 26 of instant application 2-chloro-5-(4-methoxyspiro[1,2-diox- etane-3,2'-(5-chloro-)tricyclo[3,3,1-1.sup.3,7]-decan]-1-yl)-1-phenyl phosphate, chloroadamant-2'-ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,- 2-dioxetane and derivatives thereof. (Claim 35 of '762).

Claim 27 of instant application is drawn modified sugars. (Claim 39 of '762)

Claim 28 of instant application is drawn to a sugar moiety of ribosyl or 2' deoxyribosyl sugar. (Claims 39 of '762)

Claim 29 of instant application is drawn to nucleotide analogs. (Claim 40 of '762).

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 22 of '762 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 22 of '762 teaches sequencing with a terminal phosphate labeled nucleotide. The use of at least 2 distinctly labeled bases taught in claim 27 of '762results in a reaction in which all nucleotides are added to the reaction mix at once, which is a preset cycle.

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. The detection allows determination of nucleotide sequences. (Claims 22 and 27 of '762).

Claim 38 of instant application is drawn to quantifying a nucleic acid sequence. (Claims 1, 4, 25 of '762).

Claim 40 of instant application is drawn to a polymerase. (Claim 22 of '762).

Claim 41 of instant application is drawn to RNA as the nucleic acid template. (Claim 26 of '762).

Claim 42 of instant application is drawn to a DNA template. (Claim 26 of '762).

Claim 43 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 26 of '762 teaches the use of DNA as a template. DNA is a natural or synthetic oligonucleotide.

Claim 44 of instant application is drawn to the use of one or more detection reagents. (claim 27 of '762).

Claim 45 of instant application is drawn to one or more additional detection reagents detectably different. (Claim 27 of '762).

Claim 46 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 28 of '762).

Claim 48 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 29 of '762).

Claim 49 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 28 of '762).

Claim 52 of instant application is drawn to modified sugars. (Claim 39 of '762).

Claim 53 of instant application is drawn to a sugar moiety of ribosyl or 2'-deoxyribosyl sugar. (Claim 39 of '762) .

Claim 54 of instant application is drawn to nucleotide analogs. (Claims 19 and 40 of of '762).

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 22 of '762 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 2 of '762 teaches sequencing with a terminal phosphate labeled nucleotide. The

use of 2 distinctly labeled bases taught in claim 27 of '762 results in a reaction in which all nucleotides are added to the reaction mix at once, which is a preset cycle.

'762 does not teach the a nucleic acid template immobilized on a solid support (claim1, 2, 32,33), a primer immobilized on a solid support (claim 1, 3, 32, 34), a primer and template hybridized then immobilized on a solid support (claim 1, 4, 32, 34), a polymerization enzyme on solid support (claim 5, 36), or a flow through system (claim 6, 37).

However, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21)(claims 1, 2, 32, 33). Target nucleic acid is interpreted as template. Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19) (claims claim 1, 3, 32, 34). Williams teaches oligonucleotides are primers (see page 29, lines 7-18). Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2) (claim 1, 4, 32, 34). Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6) (claims 5 and 36). Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29) (claims 6 and 37). Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides (see abstract).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of immobilization and flow cells taught by Williams to improve the methods of detection taught by US Patent 7033762,

because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides. The ordinary artisan would be motivated to use the flow cell and immobilization of Williams because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides.

12. Claims 1-6,9, 10, 12-34, 38, 40-43, 47-49, 55-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6, 7, 12-21, 23, 26, 27, 30, 34, 36, 40, 43, 44, 46, 47, 49, 56-58 of copending Application No. 10/113030 in view of Williams et al (WO/2001/94609). Although the conflicting claims are not identical, they are co-extensive in scope.

This is a provisional obviousness-type double patenting rejection.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. Claim 26 of '030 teaches a method of detecting a target sequence by an enzyme catalyzed release of polyphosphate. Claim 1 and 26 of '030 teaches a method of sequencing by polymerization and detection of polyphosphate. Claim 2 and 27 of '030 teaches the use of a phosphatase or polyphosphate transferring enzyme.

Claim 9 of instant application is drawn to a polymerase. Claim 13, 36 of '030 teaches the use of a DNA polymerase.

Claim 10 of instant application is drawn to RNA as the nucleic acid template. (Claim 3 of '030).

Claim 11 of instant application is drawn to a DNA template. Claim 12, 26 of '030.

Claim 12 of instant application is drawn to a synthetic or natural oligonucleotide. Claima 12 and 34 of '030 teaches the use of DNA. DNA is a natural or synthetic oligonucleotide.

Claim 13 of instant application is drawn to the simultaneous conducting and subjecting steps. Claim 2 of '030 teaches the polymerase reaction in the presence of a phosphatase, which would result in simultaneous conducting and subjecting steps.

Claim 14 of instant application is drawn to polyphosphates with 4 or more phosphates in the polyphosphate chain. (Claim 7 of '030)

Claim 15 of instant application is drawn to the detectable species produced being substantially proportional to the amount of nucleic acid sequence. (Claim 33 of '030).

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. (claim 1 of '030).

Claim 17 of instant application is drawn to including one of more detectable agents in the polymerization reaction. (claim 14 of '030).

Claim 18 of instant application is drawn to one or more additional detection reagents detectably different. (Claim 15 of '030).

Claim 19 of instant application is drawn to an antibody. (Claim 16 of '030).

Claim 20 of instant application is drawn to detectable species from the group of consisting of color, fluorescence emission, chemiluminescence, mass change, reduction/oxidation potential and combinations thereof. (Claim 17, 40, 58 of '030).

Claim 21 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 6, 30 of '030).

Claim 22 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 17, 40, 58 of '030).

Claim 23 of instant application is drawn to fluorogenic dyes. (Claim 19, 45 of '030).

Claim 24 of instant application is drawn to 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate or derivative thereof. (Claim 20, 43 of '030).

Claim 25 of instant application is drawn to a phosphatase activated 1, 2-dioxetane compound. (Claim 21, 44 of '030).

Claim 26 of instant application 2-chloro-5-(4-methoxyspiro[1,2-diox- etane-3,2'-(5-chloro-)tricyclo[3,3,1-1.sup.3,7]-decan]-1-yl)-1-phenyl phosphate, chloroadamant-2'-ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,- 2-dioxetane and derivatives thereof. (Claim 19 and 45 of '030).

Claim 27 of instant application is drawn to modified sugars. (Claims 23,46, 56 of '030).

Claim 28 of instant application is drawn to a sugar moiety of ribosyl or 2' deoxyribosyl sugar (claims 23,46, 56 of '030).

Claim 29 of instant application is drawn to nucleotide analogs. (Claims 24,47,57 of '030)

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 1, 2, 26 of '030 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 26 of '030 teaches sequencing with a terminal phosphate labeled nucleotide.

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. The detection allows determination of nucleotide sequences. (claim 26 of '030).

Claim 38 of instant application is drawn to quantifying a nucleic acid sequence. (claims 49 of '030).

Claim 39 of instant application is drawn quantitating nucleic acid sequence by comparison to standards. (Claim 49 of '030).

Claim 40 of instant application is drawn to a polymerase. (claim 13, 36 of '030).

Claim 41 of instant application is drawn to RNA as the nucleic acid template. (Claim 3 of '030)

Claim 42 of instant application is drawn to a DNA template. (Claim 12, 26, 34, 35 of '030).

Claim 43 of instant application is drawn to a synthetic or natural oligonucleotide. (Claim 34 of '030.)

Claim 47 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 15 of '030).

Claim 48 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 12 of '030).

Claim 49 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 15 of '030).

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 22 of '030 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 26 of '030 teaches sequencing with a terminal phosphate labeled nucleotide.

Application number 10/113030 does not teach the a nucleic acid template immobilized on a solid support (claim1, 2, 32,33), a primer immobilized on a solid support (claim 1, 3, 32, 34), a primer and template hybridized then immobilized on a solid support (claim 1, 4, 32, 34), a polymerization enzyme on solid support (claim 5, 36), or a flow through system (claim 6, 37).

However, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21)(claims 1, 2, 32, 33). Target nucleic acid is interpreted as template. Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19) (claims claim 1, 3, 32, 34). Williams teaches oligonucleotides are primers (see page 29, lines 7-18). Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2) (claim 1, 4, 32, 34). Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6) (claims 5 and 36). Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29) (claims 6 and 37). Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides (see abstract).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of immobilization and flow cells taught by Williams to improve the methods of detection taught by application number 10/113030, because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated

nucleotides. The ordinary artisan would be motivated to use the flow cell and immobilization of Williams because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides.

13. Claims 1-6, 9-16, 20-38, 40-45, 47-49, 55-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6,12, 15, 17-20, 22, 25, 26, 28-30, 34, 40, 58, 64 of copending Application No. 10/113025 in view of Williams et al (WO/2001/94609). Although the conflicting claims are not identical, they are coextensive in scope.

This is a provisional obviousness-type double patenting rejection.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. Claim 26 of '025 teaches a method of detecting a target sequence by an enzyme catalyzed release of polyphosphate. Claim 3 of '025 teaches polyphosphate undergoes a chemical change by phosphatase.

Claim 9 of instant application is drawn to a polymerase. (Claim 26 of '025).

Claim 10 of instant application is drawn to RNA as the nucleic acid template. (Claim 26 of '025).

Claim 11 of instant application is drawn to a DNA template. (Claim 4 of '025).

Claim 12 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 4 of '025 teaches the use of nucleic acid target, which includes DNA. DNA is a natural or synthetic oligonucleotide.

Claim 13 of instant application is drawn to the simultaneous conducting and subjecting steps. Claim 26 of '025 teaches the polymerase reaction in the presence of a phosphatase, which would result in simultaneous conducting and subjecting steps.

Claim 14 of instant application is drawn to polyphosphates with 4 or more phosphates in the polyphosphate chain. (Claim 12 of '025)..

Claim 15 of instant application is drawn to the detectable species produced being substantially proportional to the amount of nucleic acid sequence. (Claim 1 of '025)

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. (Claim 22 of '025).

Claim 20 of instant application is drawn to detectable species. (Claim 15 of '025).

Claim 21 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (claim 12 of '025).

Claim 22 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 15 of '025).

Claim 23 of instant application is drawn to fluorogenic dyes. (Claim 18 of '025).

Claim 24 of instant application is drawn to 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate or derivative thereof. (claim 19 of '025).

Claim 25 of instant application is drawn to a phosphatase activated 1, 2-dioxetane compound. (Claim 20 of '025).

Claim 26 of instant application 2-chloro-5-(4-methoxyspiro[1,2-diox- etane-3,2'-(5-chloro-)tricyclo[3,3,1-1.sup.3,7]-decan]-1-yl)-1-phenyl phosphate, chloroadamant-2'-ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,- 2-dioxetane and derivatives thereof. Claim 18 of '025.

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 26 of '025 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 26 of '025 teaches sequencing with a terminal phosphate labeled nucleotide.

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. The detection allows determination of nucleotide sequences. Claims 26 of '025 teach a method of sequencing by polymerization and detection of a reaction product.

Claim 38 of instant application is drawn to quantifying a nucleic acid sequence. (Claims 1, 22, 25, 28 of '025).

Claim 40 of instant application is drawn to a polymerase. (Claim 26 of '025).

Claim 41 of instant application is drawn to RNA as the nucleic acid template. Claim 4 of '025 teaches a nucleic acid template, RNA is a nucleic acid.

Claim 42 of instant application is drawn to a DNA template. Claim 4 of '025 teaches a nucleic acid template, DNA is a nucleic acid.

Claim 43 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 34 of '025 teaches a nucleic acid template, DNA is a nucleic acid. DNA is a natural or synthetic oligonucleotide.

Claim 44 of instant application is drawn to the use of one or more detection reagents. (Claim 4 of '025)

Claim 45 of instant application is drawn to one or more additional detection reagents detectably different. (Claim 4 of '025)

Claim 47 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. Claim 17, 29, 40, 58 of '025 .

Claim 48 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 6, 30, 53, 64 of '025.)

Claim 49 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 17, 29, 40, 58 of '025)

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 26 of

'025 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 26 of '025 teaches sequencing with a terminal phosphate labeled nucleotide.

Application number 10/113025 does not teach the a nucleic acid template immobilized on a solid support (claim1, 2, 32, 33), a primer immobilized on a solid support (claim 1, 3, 32, 34), a primer and template hybridized then immobilized on a solid support (claim 1, 4, 32, 34), a polymerization enzyme on solid support (claim 5, 36), or a flow through system (claim 6, 37).

However, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21)(claims 1, 2, 32, 33). Target nucleic acid is interpreted as template. Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19) (claims claim 1, 3, 32, 34). Williams teaches oligonucleotides are primers (see page 29, lines 7-18). Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2) (claim 1, 4, 32, 34). Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6) (claims 5 and 36). Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29) (claims 6 and 37). Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides (see abstract).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of immobilization and flow cells taught by Williams to improve the methods of detection taught by '025, because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides. The ordinary artisan would be motivated to use the flow cell and immobilization of Williams because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides.

14. Claims 1-6, 9-16, 20-26, 31-33, 36-45, 47-49, 55-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim1, 3, 4, 12-14, 18-24, 26- 28, 30, 32, 34 of copending Application No. 10651362 in view of Williams et al (WO/2001/94609). Although the conflicting claims are not identical, they are coextensive in scope

This is a provisional obviousness-type double patenting rejection.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. Claim 23 of '362 teaches a method of detecting a target sequence by an enzyme catalyzed release of polyphosphate. Claim 24 of '362 teaches polyphosphate undergoes a chemical change by phosphatase. Application

number 10651362 teaches detection of a nucleotide sequence by polymerization by the release of a polyphosphate by phosphatase cleaveage.

Claim 9 of instant application is drawn to a polymerase. (claim 3 of '362).

Claim 10 of instant application is drawn to RNA as the nucleic acid template. Claim 1 of '362 teaches nucleic acids, RNA is a nucleic acid. Further claim 27 of '362, teaches the use of reverse transcriptase which is RNA dependent.

Claim 11 of instant application is drawn to a DNA template. Claim 3 of '362 teaches the use of DNA polymerase, which requires DNA as a template.

Claim 12 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 1 of '362 teaches the use of nucleic acid target, which includes DNA. DNA is a natural or synthetic oligonucleotide.

Claim 13 of instant application is drawn to the simultaneous conducting and subjecting steps. (Claim 26 of '362).

Claim 14 of instant application is drawn to polyphosphates with 4 or more phosphates in the polyphosphate chain. (Claim 13 of '362).

Claim 15 of instant application is drawn to the detectable species produced being substantially proportional to the amount of nucleic acid sequence. (Claim 30 of '362)

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. (claim 24, 28 of '362).

Claim 20 of instant application is drawn to detectable species. (Claim 18 of '362).

Claim 21 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 14 of '362.)

Claim 22 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 18 of '362).

Claim 23 of instant application is drawn to fluorogenic dyes. (Claim 19 of '362.)

Claim 24 of instant application is drawn to 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate or derivative thereof. (Claim 20 of '362).

Claim 25 of instant application is drawn to a phosphatase activated 1, 2-dioxetane compound. (Claims 21, 22 of '362).

Claim 26 of instant application 2-chloro-5-(4-methoxyspiro[1,2-diox- etane-3,2'-(5-chloro-)tricyclo[3,3,1-1.sup.3,7]-decan]-1-yl)-1-phenyl phosphate, chloroadamant-2'-ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,- 2-dioxetane and derivatives thereof. (Claim 22 of '362).

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 23 of '362 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. (claim 23 of '362).

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. The detection allows determination of nucleotide sequences. Claims 23 of '362 .

Claim 38 of instant application is drawn to quantifying a nucleic acid sequence. claims 30 of '362 .

Claim 40 of instant application is drawn to a polymerase. (claim 3, 4, 27 of '362)

Claim 41 of instant application is drawn to RNA as the nucleic acid template. Claim 1 of '362 teaches nucleic acids, RNA is a nucleic acid. Further claim 27 of '362, teaches the use of reverse transcriptase which is RNA dependent .

Claim 42 of instant application is drawn to a DNA template. Claim 1 of '362 teaches a nucleic acid template, DNA is a nucleic acid. DNA polymerase requires DNA as a template.

Claim 43 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 1 of '362 teaches a nucleic acid template, DNA is a nucleic acid. DNA is a natural or synthetic oligonucleotide.

Claim 44 of instant application is drawn to the use of one or more detection reagents. Claim 12 of '362.

Claim 45 of instant application is drawn to one or more additional detection reagents detectably different. Claim 23 of '362.

Claim 47 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. Claim 18 of '362 .

Claim 48 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. Claim 14, 33 of '362.

Claim 49 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. claim 18 of '362.

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 23 of '362 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. Claim 23 of '362 teaches sequencing with a terminal phosphate labeled nucleotide.

Application number 10651362 does not teach the a nucleic acid template immobilized on a solid support (claim 1, 2, 32, 33), a primer immobilized on a solid support (claim 1, 3, 32, 34), a primer and template hybridized then immobilized on a solid support (claim 1, 4, 32, 34), a polymerization enzyme on solid support (claim 5, 36), or a flow through system (claim 6, 37).

However, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21)(claims 1, 2, 32, 33). Target nucleic acid is interpreted

as template. Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19) (claims claim 1, 3, 32, 34). Williams teaches oligonucleotides are primers (see page 29, lines 7-18). Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2) (claim 1, 4, 32, 34). Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6) (claims 5 and 36). Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29) (claims 6 and 37). Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides (see abstract).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of immobilization and flow cells taught by Williams to improve the methods of detection taught by application number 10651362, because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides. The ordinary artisan would be motivated to use the flow cell and immobilization of Williams because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides.

15. Claims 1-6, 9-16, 20-26, 30-34, 36-38, 40, 41-45, 47-49, 55-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 6, 9, 11, 15, 16, 17, 18, 21, 23, 26, 27, 28, 29, 30, 36, of

copending Application No. 10651582 in view of Williams et al (WO/2001/94609). Although the conflicting claims are not identical, they are coextensive in scope.

This is a provisional obviousness-type double patenting rejection.

Claim 1 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is reacted with a phosphatase and detected. The detection allows determination of nucleotide sequences. Claim 1 of '582 teaches a method of detecting a target sequence by an enzyme catalyzed release of polyphosphate. Claim 4 of '582 teaches a phosphatase.

Claim 9 of instant application is drawn to a polymerase. (Claim 11 of of '582).

Claim 10 of instant application is drawn to RNA as the nucleic acid template. (Claim 11 of '582).

Claim 11 of instant application is drawn to a DNA template. (Claim 9 of '582). Claim 12 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 9 of '582 teaches the use of nucleic acid target, which includes DNA. DNA is a natural or synthetic oligonucleotide.

Claim 13 of instant application is drawn to the simultaneous conducting and subjecting steps. (Claim 6 of '582).

Claim 14 of instant application is drawn to polyphosphates with 4 or more phosphates in the polyphosphate chain. (Claim 17 of '582).

Claim 15 of instant application is drawn to the detectable species produced being substantially proportional to the amount of nucleic acid sequence. (claim 16 of '582).

Claim 16 of instant application is drawn to the use of a phosphatase or another phosphate transferring enzyme. (Claim 4 of '582).

Claim 20 of instant application is drawn to detectable species. (Claim 15 of '582).

Claim 21 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 23 of '582).

Claim 22 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 15 of '582).

Claim 23 of instant application is drawn to fluorogenic dyes. (Claim 27 of '582).

Claim 24 of instant application is drawn to 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate or derivative thereof. (claim 28 of '582).

Claim 25 of instant application is drawn to a phosphatase activated 1, 2-dioxetane compound. (Claim 29 of '582).

Claim 26 of instant application 2-chloro-5-(4-methoxyspiro[1,2-diox- etane-3,2'-(5-chloro-)tricyclo[3,3,1-1.sup.3,7]-decan]-1-yl)-1-phenyl phosphate, chloroadamant-2'-ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,- 2-dioxetane and derivatives thereof. (Claim 27, 30 of '582).

Claim 30 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. (Claim 36 of '582).

Claim 31 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. (Claim 36 of '582).

Claim 32 of instant application is drawn to conducting a polymerization reaction on a solid support in which a terminal phosphate labeled nucleoside is incorporated onto a primer strand of DNA complementary to the template strand. The terminal labeled phosphate is detected. The detection allows determination of nucleotide sequences. (Claim 36 of '582).

Claim 38 of instant application is drawn to quantifying a nucleic acid sequence. (Claim 16 of '582).

Claim 40 of instant application is drawn to a polymerase. (claim 11 of '582).

Claim 41 of instant application is drawn to RNA as the nucleic acid template. (Claim 9 of '582).

Claim 42 of instant application is drawn to a DNA template. Claim 9 of '582 teaches a nucleic acid template, DNA is a nucleic acid. DNA polymerase requires DNA as a template.

Claim 43 of instant application is drawn to a synthetic or natural oligonucleotide. Claim 9 of '582 teaches a nucleic acid template, DNA is a nucleic acid. DNA is a natural or synthetic oligonucleotide.

Claim 44 of instant application is drawn to the use of one or more detection reagents. (Claim 21 of '582).

Claim 45 of instant application is drawn to one or more additional detection reagents detectably different. Claim 21 of '582 teaches the use of 1 or more additional detection reagents. The distinct labels are interpreted as detectably different.

Claim 47 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 26 of '582).

Claim 48 of instant application is drawn to a method of using a terminal phosphate labeled nucleotide of the recited structure. (Claim 23 of '582).

Claim 49 of instant application is drawn to the use of chemiluminescent compounds, fluorogenic or fluorescent dyes, chromogenic or colored dyes, mass tags, electrochemical tags. (Claim 18 of '582).

Claim 55 of instant invention is drawn to the ordered addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction. Claim 36 of '582 teaches sequencing with a terminal phosphate labeled nucleotide. Sequencing is the ordered incorporation of nucleotides.

Claim 56 of instant invention is drawn to the addition of terminal phosphate labeled polyphosphate nucleosides to a polymerase reaction in a preset schedule. (claim 36 of '582).

'582 does not teach the a nucleic acid template immobilized on a solid support (claim 1, 2, 32, 33), a primer immobilized on a solid support (claim 1, 3, 32, 34), a

primer and template hybridized then immobilized on a solid support (claim 1, 4, 32, 34), a polymerization enzyme on solid support (claim 5, 36), or a flow through system (claim 6, 37).

However, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21)(claims 1, 2, 32, 33). Target nucleic acid is interpreted as template. Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19) (claims claim 1, 3, 32, 34). Williams teaches oligonucleotides are primers (see page 29, lines 7-18). Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2) (claim 1, 4, 32, 34). Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6) (claims 5 and 36). Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29) (claims 6 and 37). Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides (see abstract).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of immobilization and flow cells taught by Williams to improve the methods of detection taught by '582, because Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides. The ordinary artisan would be motivated to use the flow cell and immobilization of Williams because

Williams teaches the flow cell and immobilization of reaction components allows for real time sequencing without interference from unincorporated nucleotides.

16. Claims 8 and 39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over, in the alternative claims 15 and 22 of '812, 1 of '839, 22 of '762 1, 2, 26, 27 of '030, 3 and 26 of '025, 24 of '362, 1 and4 of '582, and Williams et al (WO/2001/94609) each further in view of Wittwer et al (US Patent 6174670). Although the conflicting claims are not identical, they are coextensive in scope.

The teachings of '812, '839, '762, '030, '025, '362, '582, and Williams et al (WO/2001/94609)are set forth above. Williams et al and '812, '839, '762, '030, '025, '362, '582, do not teach the quantifying nucleic acid by comparing spectra with a known standard.

However, Wittwer teaches determining the concentration of a nucleic acid by comparison to the fluorescence of a known concentration template (see column 11, line 65 to column 12 line 40). Wittwer teaches this simple method allows quantification of low copy number DNA (see column 39, lines 59-60).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to use the quantitate the nucleic acid sequences of of '812, '839, '762, '030, '025, '362, '582, and Williams with Wittwers method of quantitation, because Wittwer teaches it is a simple method for quantification of low copy number DNA. The ordinary artisan would be motivated to improve the sequencing of '812,

'839, '762, '030, '025, '362, '582, and Williams method of sequencing because Wittwer teaches a simple method for quantification of low copy number DNA.

17. Claims 19 and 46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over in the alternative claims 15 and 22 of '812, 1 of '839, 22 of '762 1, 2, 26, 27 of '030, 3 and 26 of '025, 24 of '362, 1 and4 of '582, and Williams et al (WO/2001/94609) each further in view of Wittwer et al (US Patent 6174670). Although the conflicting claims are not identical, they are coextensive in scope.

The teachings of '812, '839, '762, '030, '025, '362, '582, and Williams et al (WO/2001/94609)are set forth above. Williams et al and '812, '839, '762, '030, '025, '362, '582, do not teach the use of an antibody as a detection reagent.

However, Lichtenwalter et al teach the use of an antibody to detect elongated nucleic acid complexes (see column 3, lines 27-30, column 3, lines 14-17), because it is a convenient and reliable diagnostic method (column 13, lines 20-21).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to use the antibodies taught by Lichtenwalter to detect the elongation products of '812, '839, '762, '030, '025, '362, '582, and Williams because Lichtenwalter teaches it is a convenient and reliable diagnostic method. The ordinary artisan would be motivated to detect Williams and '812, '839, '762, '030, '025, '362, '582, elongation products with Lichtenwalter's antibodies because Lichtenwalter teaches it is a convenient and reliable diagnostic method.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEHANNE SITTON
PRIMARY EXAMINER
9/29/06